

[CASE REPORT]

An Unusual Case of Acute Cholecystitis with Amyloidosis: A Case Report and Literature Review

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Abstract:

We present an extremely rare case of amyloid A (AA) deposition in the gallbladder and review the literature on similar cases. The patient was a 76-year-old man who had been diagnosed with mild bronchiectasis three years previously, who was admitted to the hospital with right upper quadrant pain and fever. Computed tomography revealed swelling and wall thickening of the gallbladder with a small gallstone. The patient was diagnosed with acute cholecystitis and cholelithiasis and underwent open cholecystectomy. A postoperative histological examination revealed extensive AA deposition in the gallbladder wall. Thus, the definitive diagnosis was acute cholecystitis with AA amyloidosis.

Key words: amyloidosis, amyloid A, acute cholecystitis

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Introduction

Amyloidosis is a rare, progressive disorder caused by the extracellular deposition of insoluble abnormal proteins that alter normal organ functions (1). Amyloidosis is usually observed as a systemic presentation; however, approximately 10% of the cases are localized (2). Amyloid deposition generally involves more than one organ and is extremely rare in the gallbladder (3, 4). Systemic amyloidosis is classified into light-chain (AL or primary), amyloid A (AA or secondary), dialysis-related, senile, and hereditary types. The production of AA protein is induced by chronic inflammatory diseases such as infections, malignancies, inflammatory bowel disease, and auto-immune disorders. We herein describe the case of a patient with AA amyloidosis due to bronchiectasis, with an unusual clinical presentation of acute cholecystitis. We also reviewed the literature to discuss previous cases of localized amyloidosis in the gallbladder.

Case Report

A 76-year-old man presented to our hospital with fever and sudden onset of right upper quadrant pain. The patient

had been diagnosed with bronchiectasis three years previously. A physical examination revealed tenderness in the right upper quadrant and a positive Murphy's sign. The patient's laboratory parameters were within the normal limits with the exception of a high white blood cell count ($14.4 \times 10^9/L$) and a high C-reactive protein level (13.74 mg/dL). Abdominal ultrasonography showed mild gallbladder wall thickening. Computed tomography (CT) of the abdomen revealed swelling and wall thickening of the gallbladder and a small gallstone (2 mm) in the gallbladder (Fig. 1A). Contrast-enhanced CT (CECT) of the abdomen revealed no focal lesion, but revealed peripheral gallbladder effusion without necrosis of the gallbladder wall (Fig. 1B). The patient was diagnosed with acute cholecystitis and underwent minimally invasive open cholecystectomy instead of laparoscopic cholecystectomy because he was receiving antiplatelet medicine for angina pectoris. Intraoperatively, the gallbladder wall was not perforated, and a small gallstone detected near the cystic duct was removed.

A postoperative examination revealed edema, ulceration, and hemorrhage in the gallbladder wall (Fig. 2A). Longitudinal sectioning of the resected gallbladder (Fig. 2B) exhibited marked thickening of the gallbladder wall, and Hematoxylin and Eosin staining revealed the infiltration of neutro-

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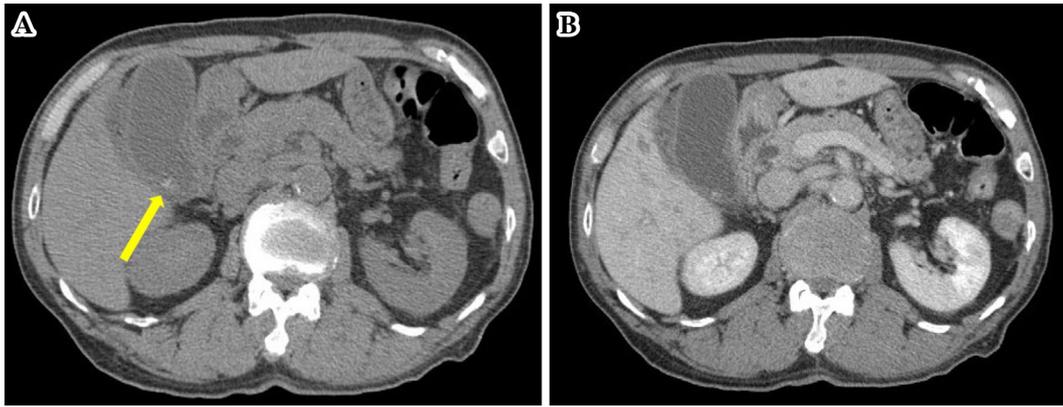


Figure 1. (A) Computed tomography reveals swelling and wall thickening of the gallbladder and a small gallstone (arrow) with no visible mass in the gallbladder. (B) Enhanced computed tomography reveals peripheral gallbladder effusion without necrosis of the gallbladder wall or a malignant lesion.

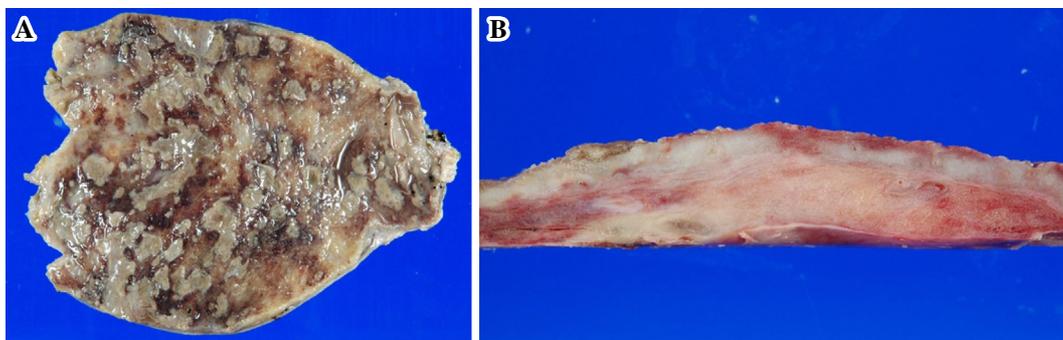


Figure 2. Macroscopic findings of the resected gallbladder. (A) In the opening along the long axis, multiple erosions and submucosal hemorrhages are observed in the body of the gallbladder. (B) On longitudinal sectioning, a markedly thickened gallbladder wall is observed in the body of the gallbladder.

phils and eosinophils in the mucosal lamina propria and eosinophilic amorphous deposition in the mucosal lamina propria and muscular layers; a similar deposition was observed around the small vascular walls of the gallbladder (Fig. 3A). The depositions were identified as AA proteins based on Dylon-staining positively (Fig. 3B) with apple-green birefringence under polarized light (Fig. 3C) and the loss of positive Dylon-staining following incubation with potassium permanganate. The patient had no signs of connective tissue disorder (*e.g.*, joint pain, skin rash, or the Raynaud phenomenon). The patient underwent esophagogastroduodenoscopy and colonoscopy, and a histopathological analysis of the tissue biopsy specimens revealed depositions of AA in the submucosa of the stomach, duodenum, terminal ileum, and colorectum. No other signs of inflammatory or malignant disease were detected, and the definitive diagnosis was AA amyloidosis due to bronchiectasis. The patient's postoperative course was uneventful, and he was discharged on postoperative day eight. After discharge, the patient was observed with conservative treatment for bronchiectasis (Fig. 4).

Discussion

Amyloidosis is a progressive, incurable, rare metabolic disease caused by the extracellular deposition of insoluble abnormal proteins that affects many organs (1). Amyloidosis can be classified as systemic or localized, and the amyloid deposition generally involves the kidneys, heart, spleen, joints, skin, and digestive tract; it rarely involves the gallbladder (3, 4). Systemic amyloidosis can be classified as light-chain (AL or primary), amyloid A (AA or secondary), dialysis-related, senile, or hereditary amyloidosis.

AA amyloidosis occurs as a result of chronic inflammatory diseases such as rheumatoid arthritis, Crohn's disease, tuberculosis, bronchiectasis, and familial Mediterranean fever (5-8). In AA amyloidosis, the expression of cytokines in response to inflammatory stimuli leads to the overproduction of serum AA (SAA) in the liver. Prolonged elevation of plasma SAA concentration results in the aggregation of amyloid into cross- β -sheet fibrillary deposits; however, the underlying mechanisms have not been completely elucidated (9, 10). SAA is not disease-specific; the quantitative SAA level is only correlated with the disease activity for the

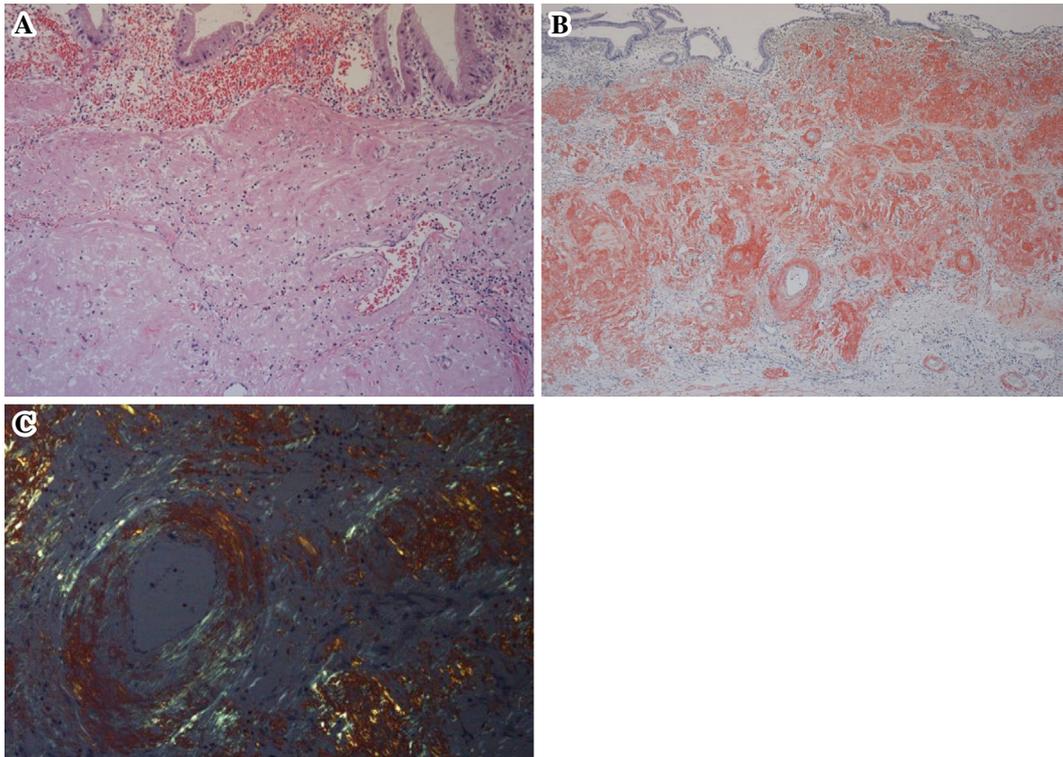


Figure 3. (A) Postoperative Hematoxylin and Eosin staining reveals infiltration of neutrophils, monocytes, and eosinophils in the mucosal lamina propria and eosinophilic amorphous deposition in the mucosal lamina propria and the muscle layers (magnification, 20×). (B) Salmon pink-colored eosinophilic deposition (Dylon staining; magnification, 40×). (C) The deposition exhibits apple-green birefringence under polarized light (magnification, 200×).

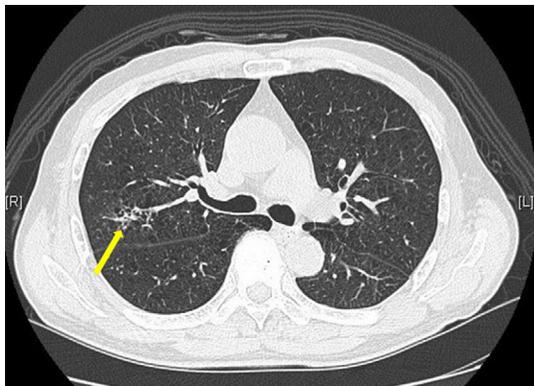


Figure 4. Computed tomography scan showing mild bronchiectasis (arrow) in the middle lobe of the right lung.

given time and is not an index of the quantity of amyloid deposition. In the present case, the deposition of AA in the gallbladder wall was considered to have developed due to bronchiectasis; however, the patient's SAA level was normal, and the patient's follow-up required investigation for potential early signs and symptoms of dysfunction of the specific organs that might be involved, including heart failure, digestive disorders, proteinuria, and multiple peripheral nerve disorders.

Our systematic search of the PubMed and JDrreamIII databases using MeSH term “cholecystitis” AND “amyloidosis”

and “gallbladder” AND “amyloidosis” revealed that the deposition of amyloid in the gallbladder has only been reported in five patients in the English literature and nine patients in the Japanese literature; the cases are summarized in Table (11-24). AA amyloidosis was reported in seven patients (50%), whereas five (36%) were diagnosed with AL amyloidosis (excluding our case). The clinical symptoms also varied among the patients, ranging from no symptoms to right upper quadrant pain, abdominal pain, epigastric pain, weight loss, fever, and symptoms of digestive tract disorder. Clinical images were not specific in any of the cases. For example, Kwon et al. reported nodular wall thickening in the body of gallbladder which was enhanced by contrast-enhanced CT, whereas Kim et al. and Tirota et al. reported mild thickening of the gallbladder on abdominal ultrasonography (11, 12, 14). In all 15 cases (including our case), a preoperative diagnosis of amyloid deposition in the gallbladder was difficult to make due to the nonspecific imaging findings of amyloid deposition in the gallbladder wall. In the case reported by Julian et al., amyloid deposition in the gallbladder wall was detected in autopsy (13). Similarly to the present case, acute calculous cholecystitis was reported in four cases (29%); however, among the other cases one case included biliary sand, and nine cases (64%) exhibited acalculous cholecystitis. Acalculous cholecystitis accounts for 2-15% of all cholecystitis cases (25); remarkably, our systematic research indicated a higher rate of acalculous

Table. Summary of the Reported Cases of Amyloidosis of the Gallbladder.

Case	Patient (Age/Sex)	Symptom	Gallstone	Imaging of GB (CT or US)	Preoperative Diagnosis	Operative Method	Amyloidosis Type	Associated Disease	Reference
Articles in English									
1	63years/F	None	-	US: focal echogenic lesion CT: nodular wall thickening	Gallbladder cancer	LC	Primary (AL)	None	(11)
2	63years/M	RUQ pain	-	US: mild wall thickening, pericholecystic infiltration	Cholecystitis	OC	Secondary (AA)	Pulmonary TB	(12)
3	80years/M	Dyspeptic	-	NS	NS	Autopsy	Primary (AL)	None	(13)
4	74years/M	RUQ pain	-	US: diffuse wall thickening with biliary sand	Cholecystitis	OC	Primary (AL)	MM	(14)
5	69years/M	RUQ pain, weight loss	-	US: diffuse wall thickening CT: wall thickening at the fungus	Cholecystitis	LC	Primary (AL)	MGUS	(15)
Articles in Japanese									
6	54years/M	Abdominal pain	-	CT: wall thickening	Cholecystitis	LC	NS	None	(16)
7	66years/M	Fever, RUQ pain	-	US: wall thickening CT: wall thickening	Cholecystitis	PTGBD→OC	Primary (AL)	MM	(17)
8	57years/F	Fever, RUQ pain	+	CT: gallstone without wall thickening	Cholecystitis	NS	Secondary (AA)	SLE	(18)
9	56years/M	Fever, RUQ pain	-	US: wall thickening CT: swelling of the gallbladder	Cholecystitis	LC	NS	CKD	(19)
10	46years/M	Abdominal pain	+	NS	Cholecystitis	NS	Secondary (AA)	DPB	(20)
11	79years/M	Abdominal pain	+	US: gallstone with wall thickening CT: swelling of the gall bladder	Cholecystitis	OC	Primary (AA)	EGC	(21)
12	64years/F	Water diarrhea	-	US: wall thickening with debris CT: swelling of the gallbladder	Necrotizing cholecystitis	OC	Secondary (AA)	RA	(22)
13	59years/F	Fever, Epigastric pain	+	US: swelling of the gallbladder with debris	Cholecystitis	NS	Secondary (AA)	RA	(23)
14	73years/F	Abdominal pain	-	CT: swelling of the gallbladder	Cholecystitis	OC	Secondary (AA)	RA	(24)

Our patient	76years/M	RUQ, fever	+	US: wall thickening CT: swelling and wall thickening	Cholecystitis	OC	Secondary (AA)	Bronchiectasis	

AA: amyloid A, AL: amyloid light chain, RUQ: right upper quadrant, GB: gallbladder, TB: tuberculosis, SLE: systemic lupus erythematosus, CKD: chronic kidney disease, DPB: diffuse panbronchiolitis, EGC: early gastric cancer, RA: rheumatoid arthritis, MM: multiple myeloma, MGUS: monoclonal gammopathy of unknown significance, LC: laparoscopic cholecystectomy, OC: open cholecystectomy, NS: not stated, CT: computed tomography, US: ultrasonography, PTGBD: percutaneous transhepatic gallbladder drainage

cholecystitis. In the present case, it was difficult to distinguish cholecystitis from cholelithiasis due to amyloid deposition in the gallbladder wall. Huffmann et al. stated that the

etiology of acute acalculous cholecystitis was multifactorial and likely resulted from bile stasis or ischemia (or both). We hypothesize that the pathophysiology of acalculous chole-

cystitis patients includes the following: 1) amyloid deposition around the small vascular wall in patients with acalculous cholecystitis can rapidly lead to ischemic changes, leading to necrotizing cholecystitis; 2) amyloid deposition in the gallbladder wall that is blocking the normal contraction of the gallbladder can lead to bile stasis, leading to direct damage of the gallbladder wall epithelium. These pathophysiological conditions can occur concomitantly or separately, and lead to the development of acalculous cholecystitis in cases with amyloid deposition on the gallbladder wall.

Treatment for AA amyloidosis aims to halt the chronic inflammatory process; however, the complete removal of the amyloid deposits from the involved organs is impossible. Morbidity in amyloidosis is related to the disease etiology as well as the extent of the functional compromise of the involved organs, and the correct diagnosis of the amyloid deposition is important for the clinical management, the prevention of misdiagnosis and potentially harmful treatment, and the assessment of the prognosis.

As the present unusual case of acute cholecystitis accompanied by amyloidosis illustrates that postoperative histologic examination reveals occasional AA deposition in the gallbladder wall in patients undergoing cholecystectomy with cholecystitis, further evaluation is important to identify and treat the etiology underlying AA amyloidosis. Preoperative clinical images that are highly suggestive of amyloid deposition in the gallbladder require further investigation.

The authors state that they have no Conflict of Interest (COI).

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